



## Editorial

## RNA-Targeting Therapies: Translating Hope



On July 20, 2016, the UK health regulator NICE published final guidance recommending the drug ataluren for children with Duchenne muscular dystrophy (DMD). This was a momentous announcement for those who had campaigned vociferously for its approval in the UK. DMD is a rare X-linked disorder that causes progressive muscular weakness. Most boys are wheelchair dependent by their early teens, and face life-threatening lung and heart complications in their 20s. DMD is usually fatal by the age of 30 years. There is no curative therapy to date; therefore there is an urgent need to develop effective targeted therapies.

Ataluren, approved by the EMA since August 2014, is expected to benefit 10–15% of boys suffering from the nonsense mutation form of the disease (nmDMD). Nonsense mutations are single nucleotide variants within the coding sequence of a gene that encodes an in-frame stop codon. Premature termination codons (PTCs) lead to short, unstable mRNA transcripts that can be degraded. Any mRNA that is transcribed will produce truncated, non-functional proteins. In the case of nmDMD, reduced levels of aberrant dystrophin make muscle fibers vulnerable to damage. Ataluren is an example of a read-through therapeutic – a chemical that selectively induces ribosomal read-through of premature, but not normal, termination codons in the mRNA. This results in the formation of stabilized mRNA and full-length, functional protein. The rationale is that although the levels of corrected functional protein are generally low due to the inability to target every muscle fiber, there may be enough present to alleviate the consequences of the pathology. Crucially, Phase III clinical results indicated that none of the children in the treatment group lost ambulation during the 48-week trial, compared to 8% treated with placebo (0 out of 47 compared to 4 of 52, NCT01826487). This demonstrated the ability of ataluren to delay loss of walking in children with nmDMD, and solidified the EMA's decision for European approval.

Read-through therapies were first described in the late 1970s when aminoglycoside antibiotics were shown to bind bacterial ribosomes and allow the insertion of amino acids at PTCs, enabling translational read-through. As 10% of inherited diseases are caused by PTC mutations, and many cancers acquire PTC mutations during their evolution, the clinical potential for using read-through therapies to treat multiple diseases is clear. In spite of promising results in cell culture, aminoglycosides *in vivo* cause nephrotoxicity and irreversible damage to cochlea hair cells. High-throughput screening approaches were undertaken by pharmaceutical and academic enterprises to identify drugs possessing read-through promoting behavior without the associated toxicity. Ataluren demonstrated translational read-through performance, low toxicity and could be delivered orally, catapulting it to lead-compound status. Ataluren is currently being tested in a number of indications including a Phase III clinical trial in patients with nonsense mutation cystic fibrosis (NCT02369731), and Phase II trials in patients with nonsense mutation aniridia (NCT02647359) and nonsense mutation Dravet syndrome or cyclin-dependent kinase-like 5 deficiency (NCT02758626).

Despite a number of favorable clinical results, a paucity of full mechanistic understanding and questionable clinical efficacy has dampened

excitement for read-through therapies in some camps. An alternative approach to correct genetic mutations by targeting RNA is to utilize the natural process of exon skipping. Exon-skipping therapies (ESTs) co-opt the natural process of pre-mRNA splicing that remove introns to leave protein-encoding exons. ESTs consist of an antisense oligonucleotide (AON) that binds to the mutated exon enabling translational machinery to skip over faulty sections of pre-mRNA. The mature mRNA comprises fewer exons, but a restored reading frame, enabling production of a slightly shorter protein. This innovative therapy does have caveats. The resultant protein must retain sufficient functionality to be able to overcome the pathology. Furthermore, intracellular delivery of AONs is a huge challenge with much research being spent in formulating conjugates that improve half-life and cell specificity. Nevertheless, the potential for broad clinical utility is reflected by a growing drug development pipeline to treat a range of disorders including DMD and neurogenetic diseases.

On September 19, 2016, the FDA controversially approved the EST eteplirsen for the treatment of DMD. Eteplirsen acts by skipping over exon 51 to produce a largely functional dystrophin protein – a strategy amenable to approximately 13% of DMD patients. The crux of this controversy was based on internal conflict at the FDA as to whether the modest increase in dystrophin levels, induced by eteplirsen, were clinically meaningful. The FDA Advisory Committee felt that flaws in the design and conduct of the available clinical trials were unable to provide reasonable evidence, and voted against approval in April 2016. However, the Director of the Center for Drug Evaluation and Research overruled this decision, recommending approval of eteplirsen under the accelerated approval pathway restricted to treat serious conditions. This decision exposed an awkward question: how much compromise should be made to accelerate approval of a potentially beneficial but clinically unproven drug? As such, the FDA has insisted that more clinical data must be obtained to demonstrate eteplirsen's efficacy. If no benefit is found, FDA approval could be withdrawn.

Both read-through therapies and ESTs use innovative strategies to target RNA and correct disease-causing mutations. However, research and development of promising compounds is extraordinarily expensive and costs must be recovered during product commercialization. Using ataluren as an example, treating a single child with nmDMD in the UK will cost £220,000 per year. Healthcare systems have to weigh up the potential gains of a drug's long-term benefits with available funds. Well-conducted and adequately powered trials are crucial to generate meaningful data to assess clinical benefit of a new drug and facilitate regulatory approval. Translational research can be a slow and expensive process but will ultimately reduce the number of ineffective drugs that are brought to market. Life-limiting diseases like DMD desperately need innovative treatment strategies, and drugs that correct RNA translation may be part of the answer.

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